Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Vaccine Updates

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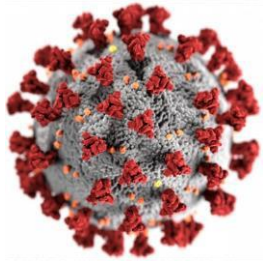
Disclosures

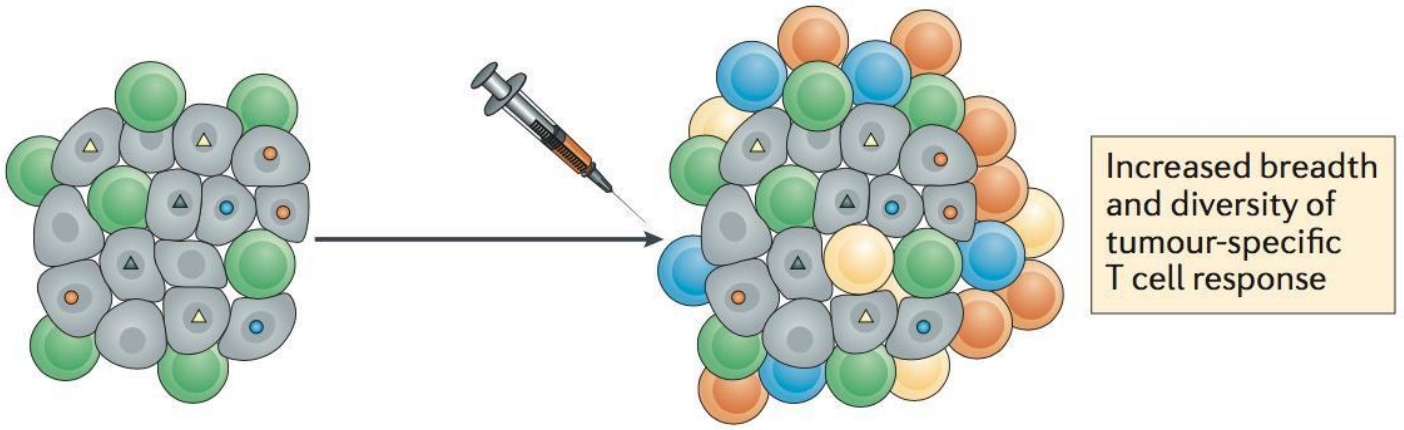
- Consulting Fees: Merck, BMS, Roche.Genentech, Celldex, Neon Therapeutics, CytomX, Novartix, Array
- Contracted Research: Medimmune/AZ, Pfizer, ArmoBiosciences
- I will be discussing non-FDA approved indications during my presentation.

SARS-CoV-2
Spike Protein



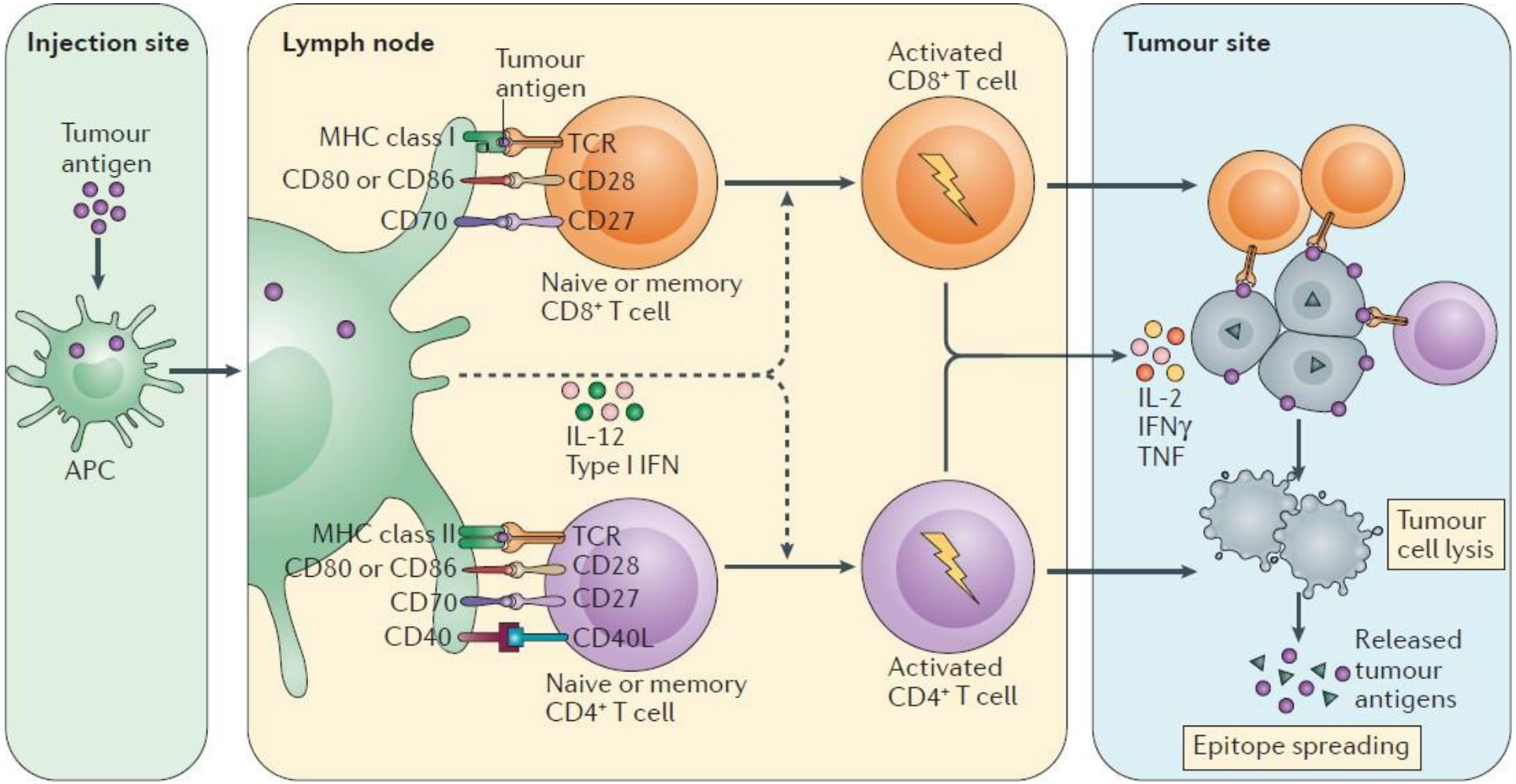
Pathogens —— **Prophylactic/Preventive vaccines**

Cancer —— **Therapeutic vaccines**



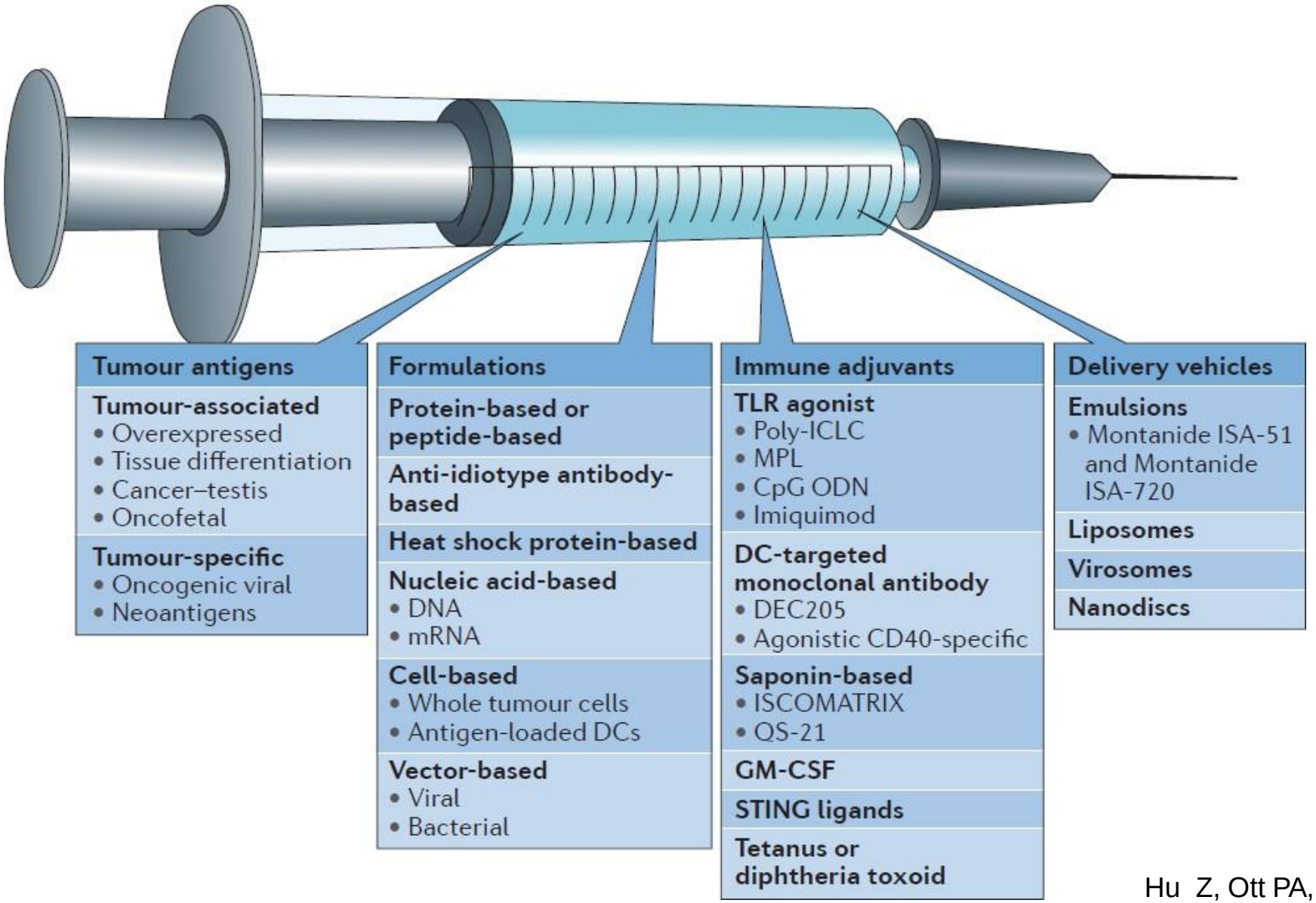
Hu Ott Wu *Nature Reviews Immunology* 2018

The Tumor Antigen Presentation Process



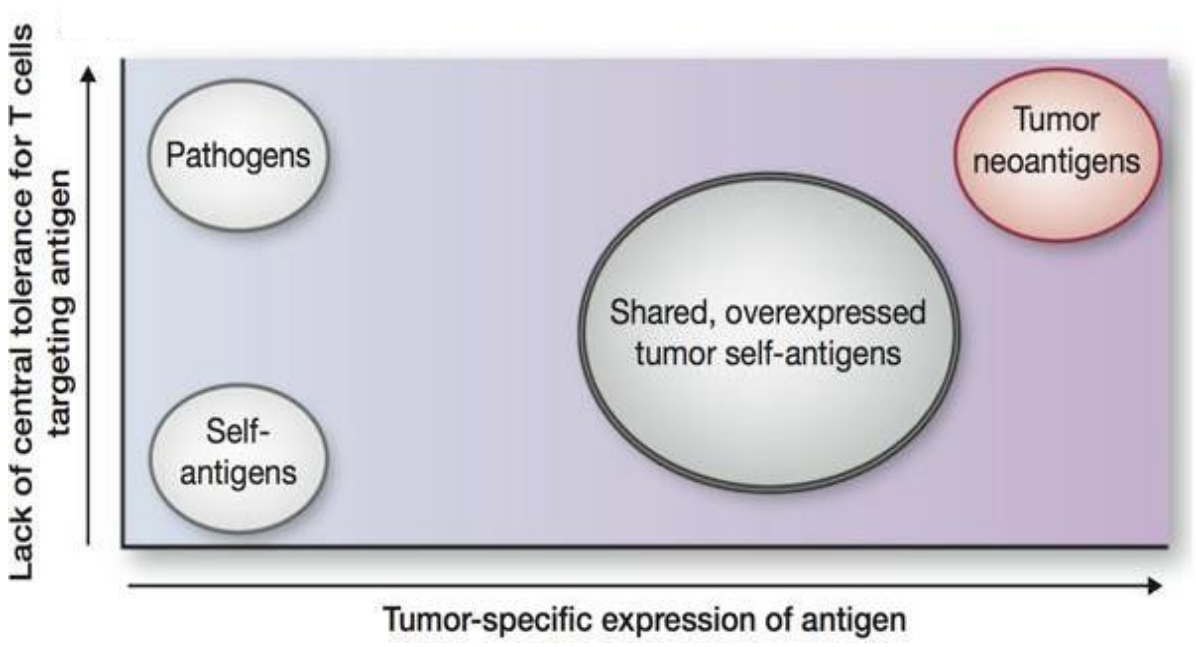
Hu Z, Ott PA, Wu CJ, *Nat. Rev. Immunol*, 2019

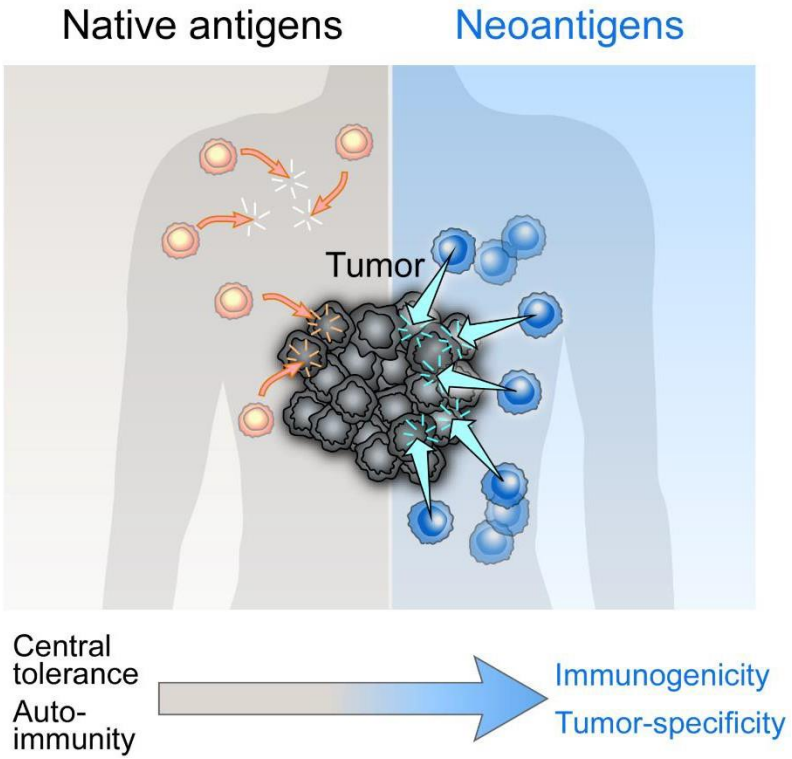
Key Components of Cancer Vaccines



Hu Z, Ott PA, Wu CJ, *Nat. Rev. Immunol*, 2019

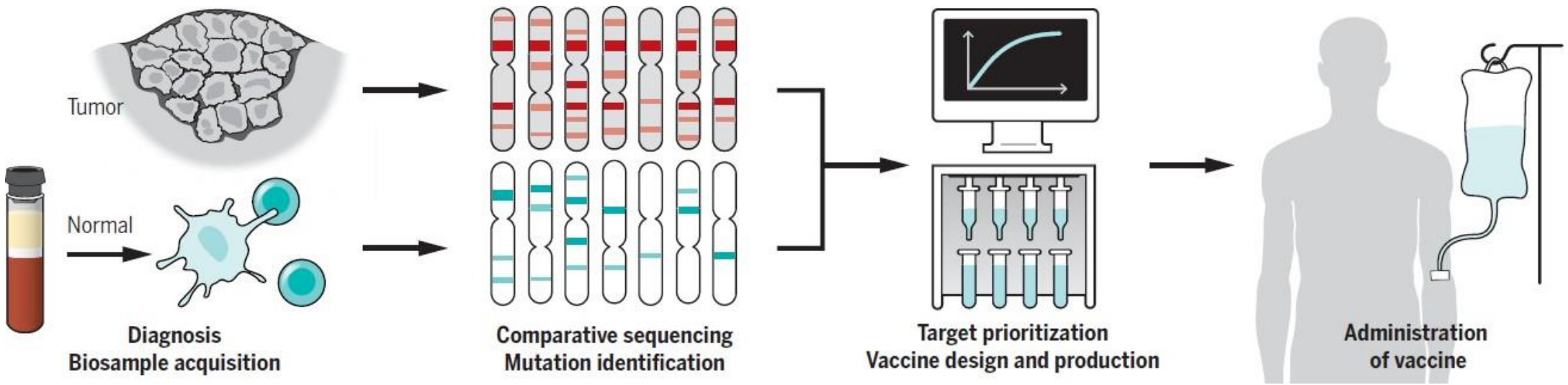
Neoantigens as Cancer Vaccine Targets: A paradigm shift





Hacohen *Cancer Immunol Res* 2013
Ott *Hematol Oncol Clin N Am* 2018

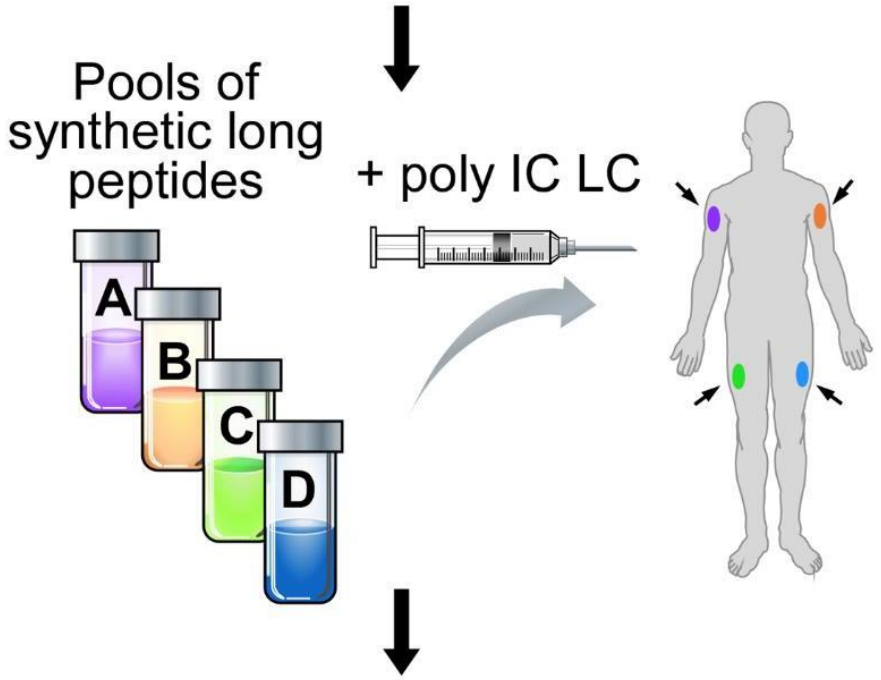
Generation of a personalized neoantigen vaccine



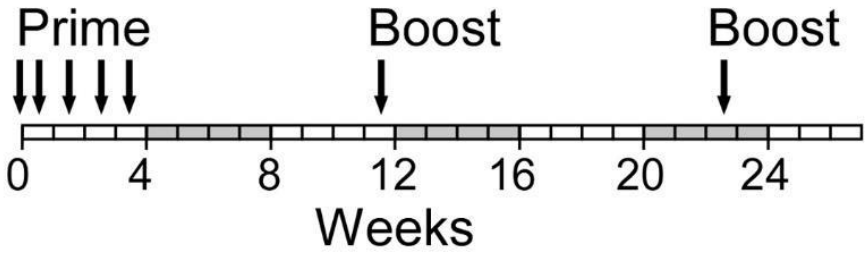
Sahin & Türeci *Science* 2018

NeoVax in High Risk Melanoma Patients: Study Design

Personal vaccine manufacture

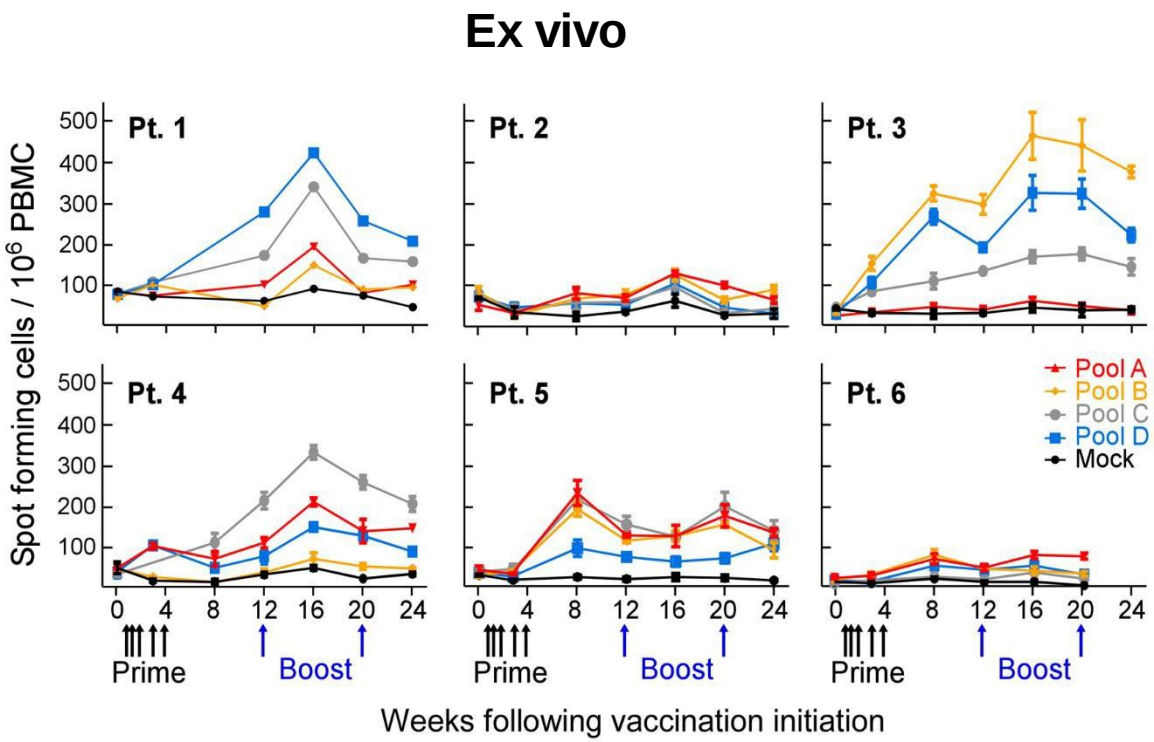


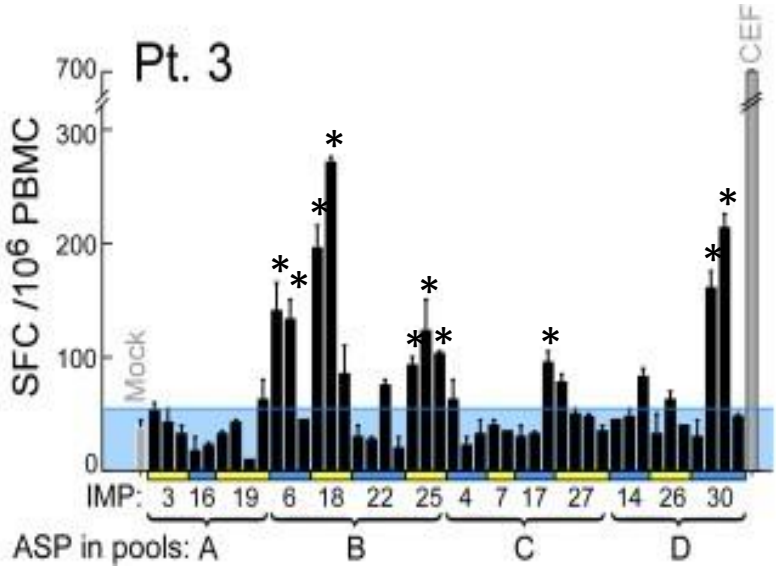
Vaccine administration



Ott et al. *Nature* 2017

Neoantigen-specific T cell responses

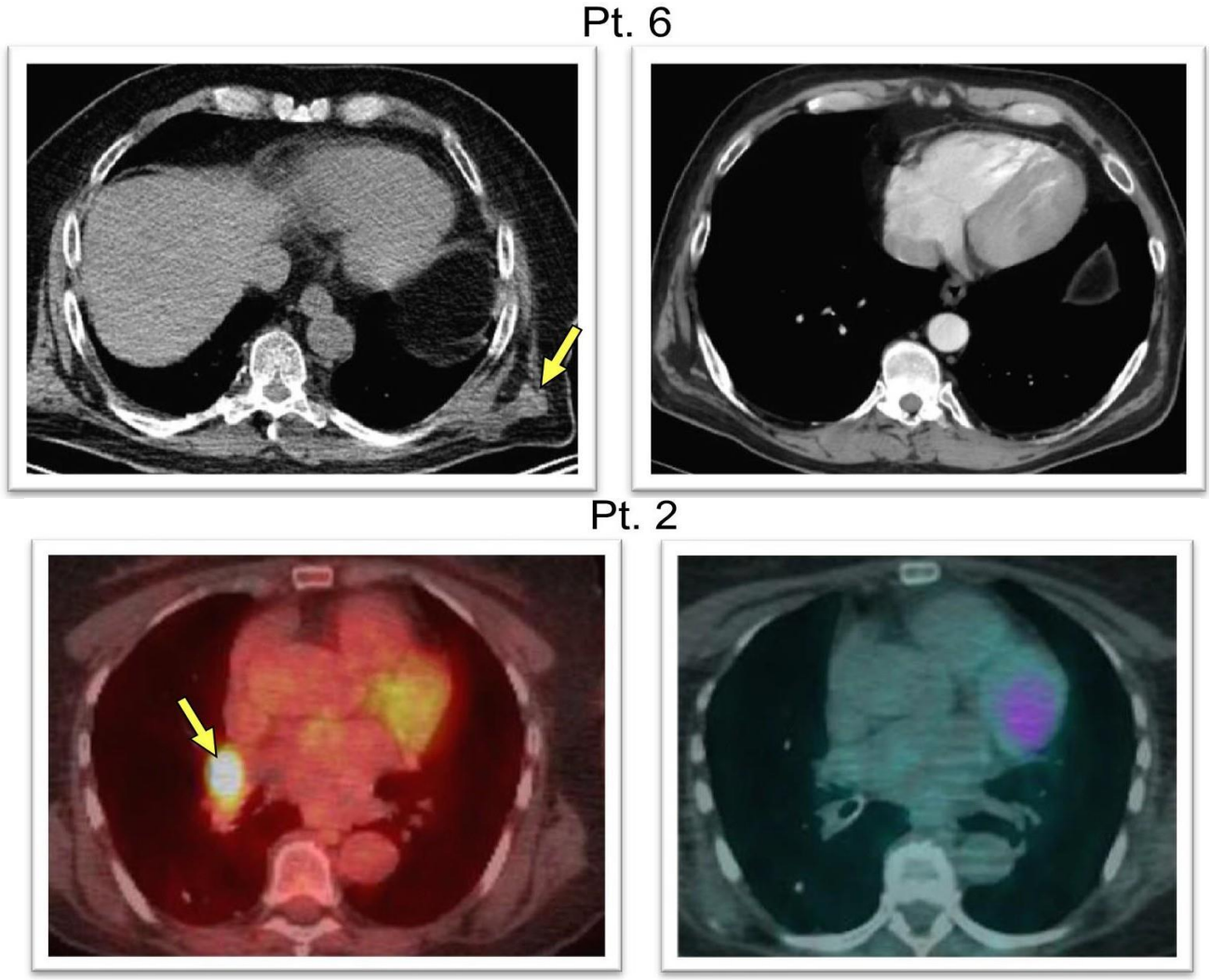




	CD4	CD8
ex vivo	18%	0%
1 stimulation	60%	16%

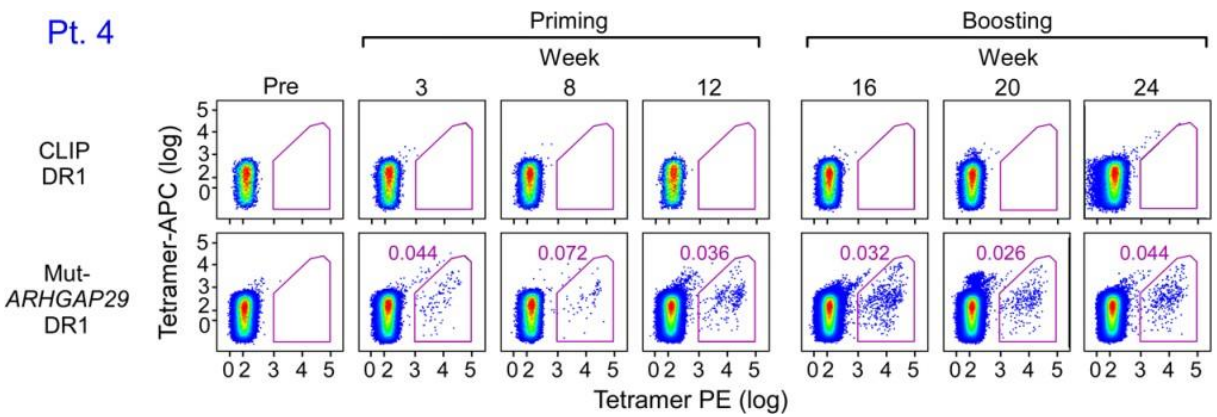
Ott et al. *Nature* 2017

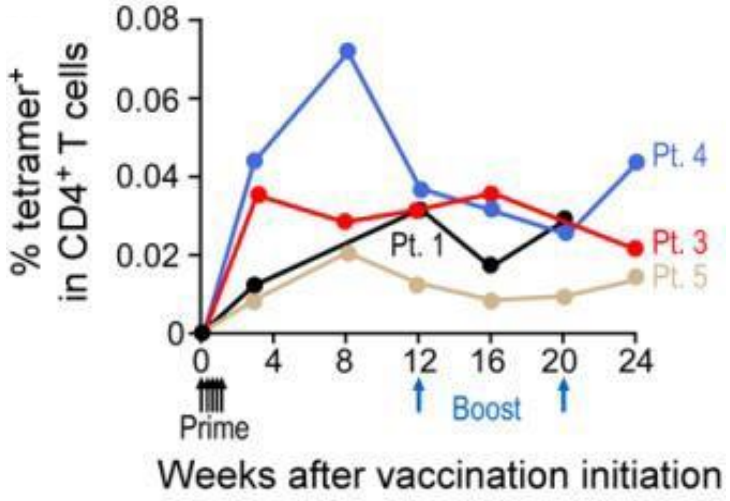
Complete responses in 2 patients who received NeoVax followed by Pembrolizumab upon recurrence



Ott et al. *Nature* 2017

Transcriptional profile of neoantigen-specific T cells over the course of vaccination





Hu Z & Leet DE *Nat. Med.*, 2021

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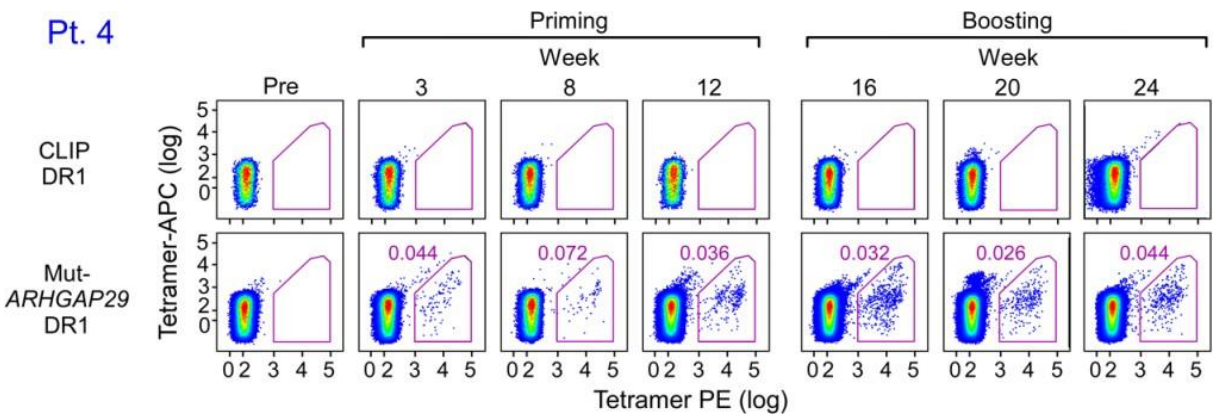

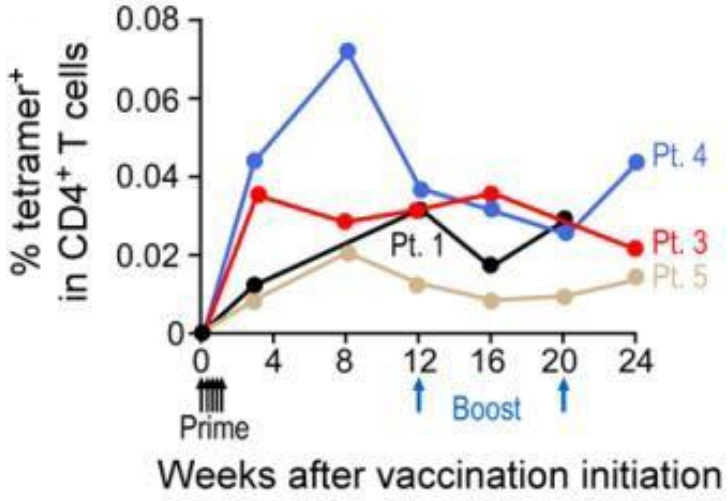

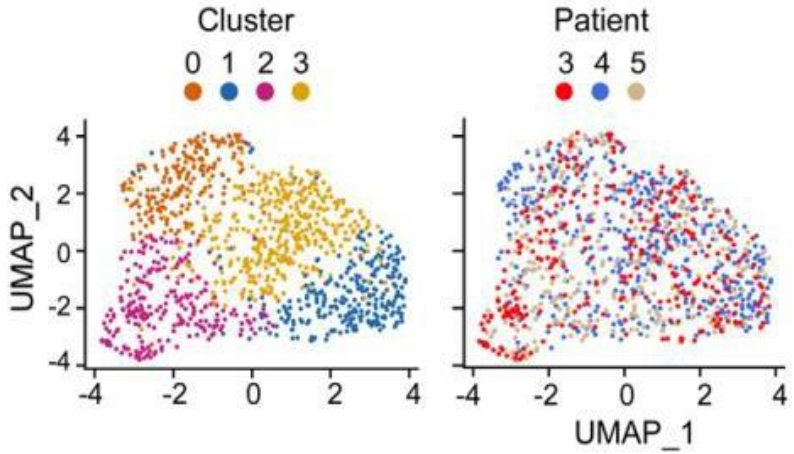

Hu Z & Leet DE *Nat. Med.*, 2021

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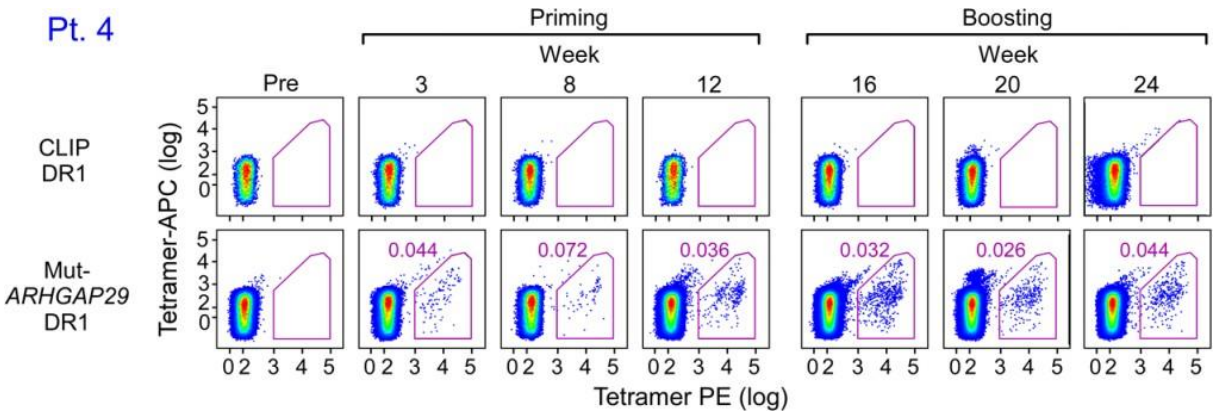
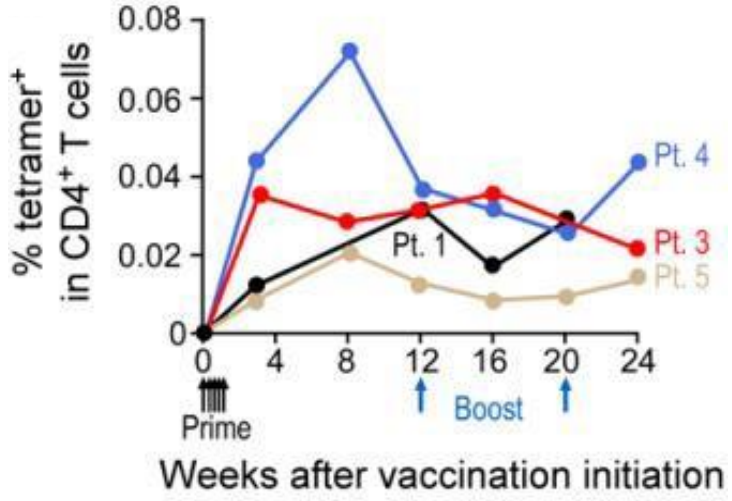
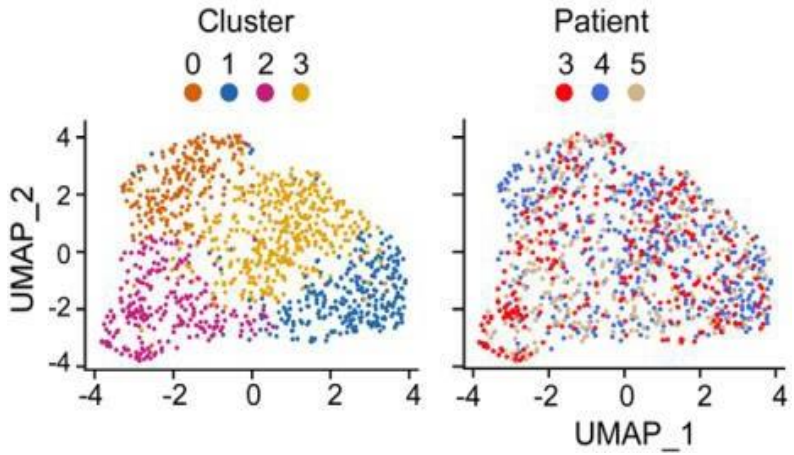
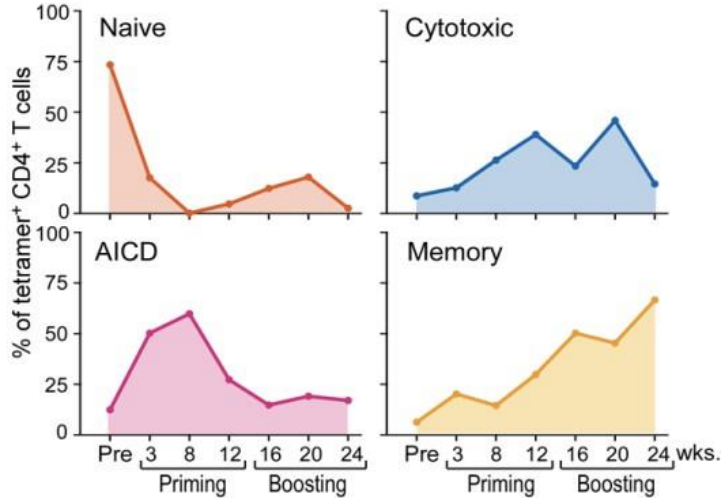


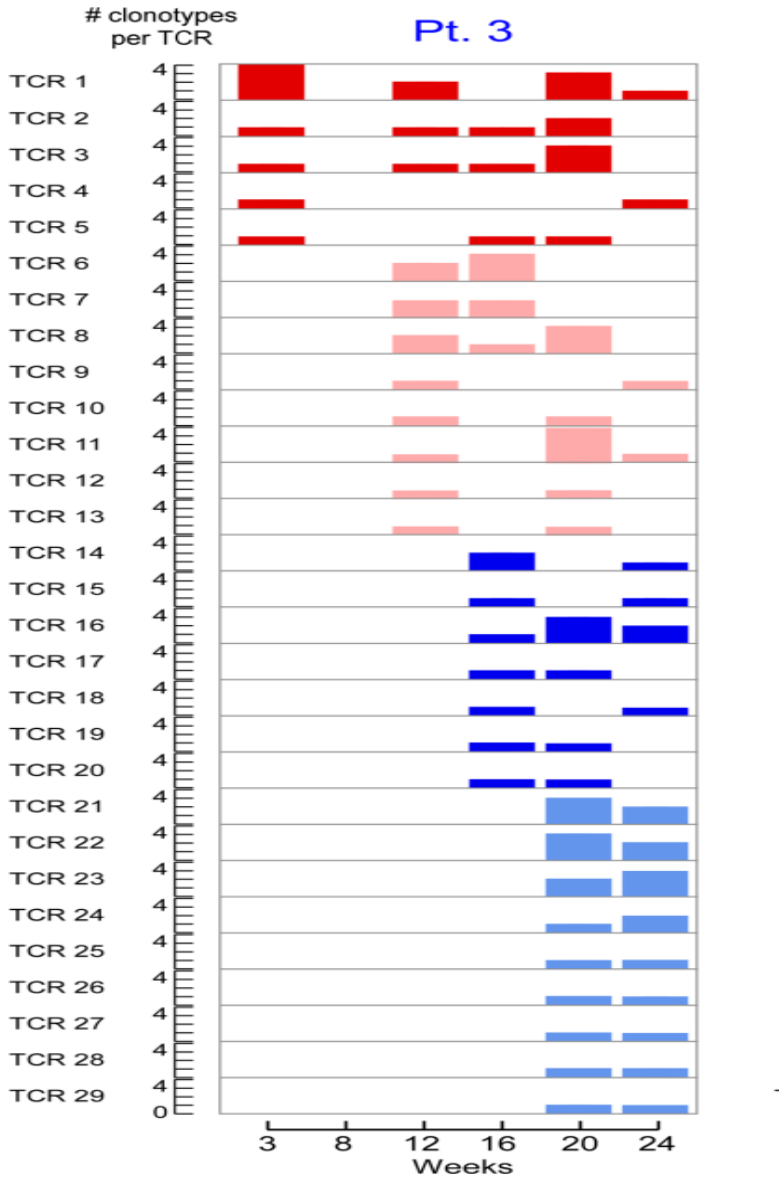






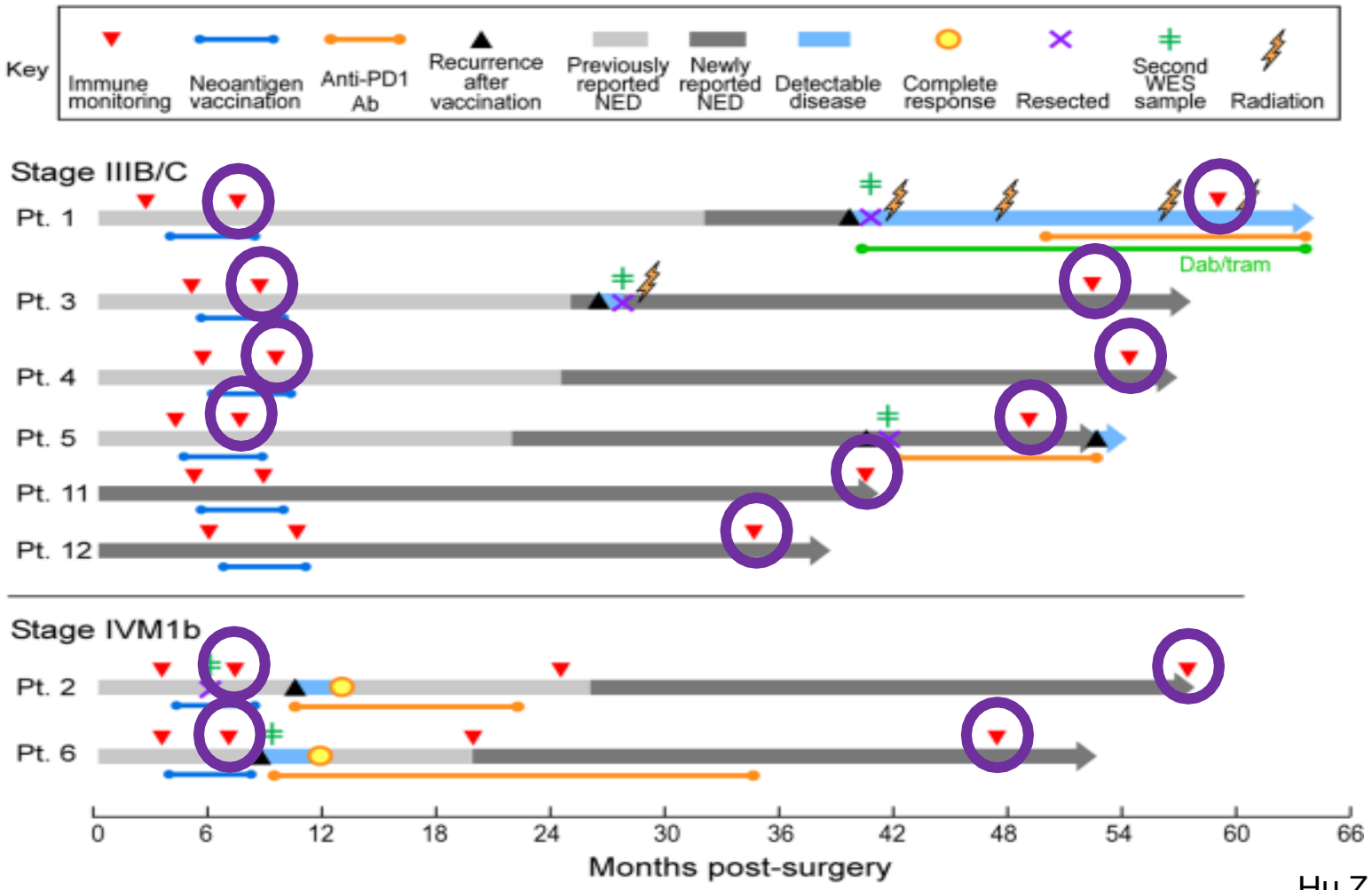
Hu Z & Leet DE *Nat. Med.*, 2021

The TCR repertoire diversifies over time after vaccination



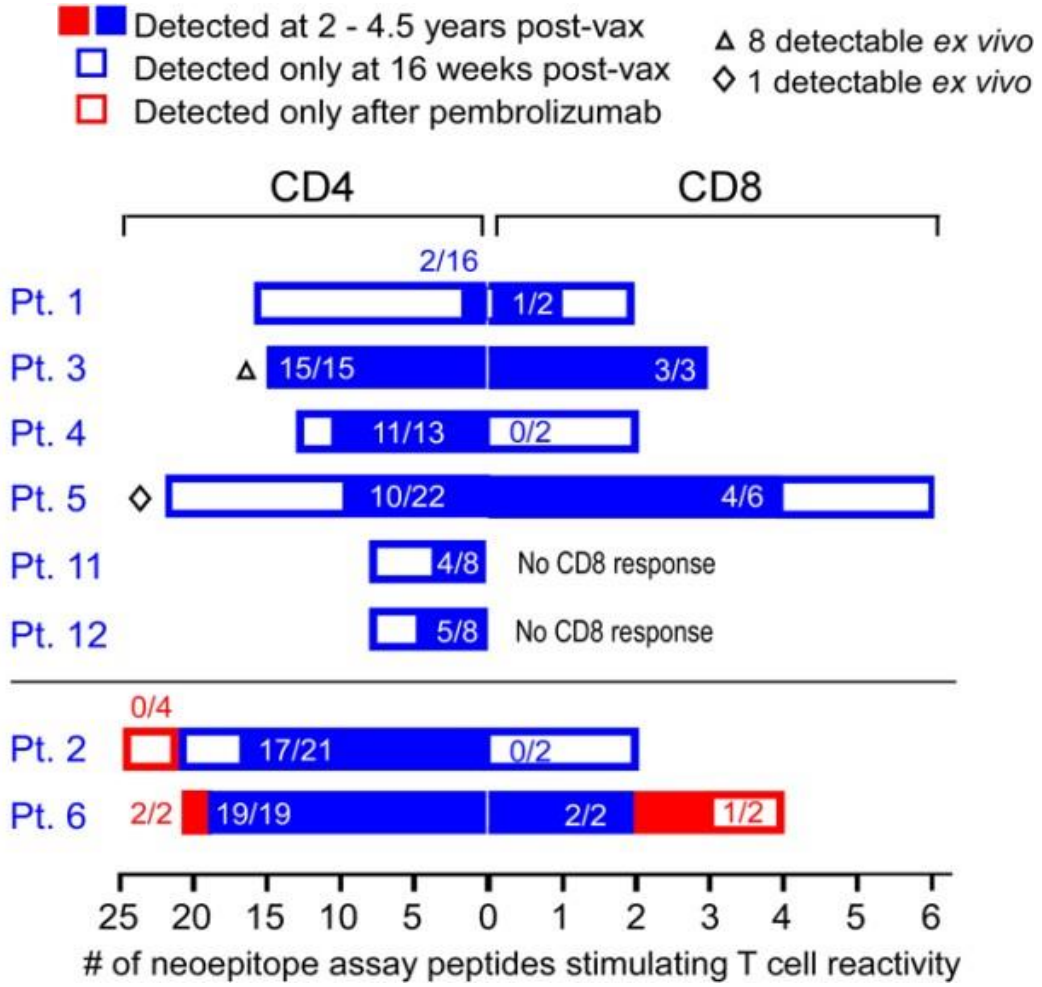
Hu Z & Leet DE *Nat. Med.*, 2021

Clinical Course of Patients with High Risk Melanoma (Long-term)



Hu Z & Leet DE *Nat. Med.*, 2021

Vaccine-induced neoantigen specific T cells persist over several years

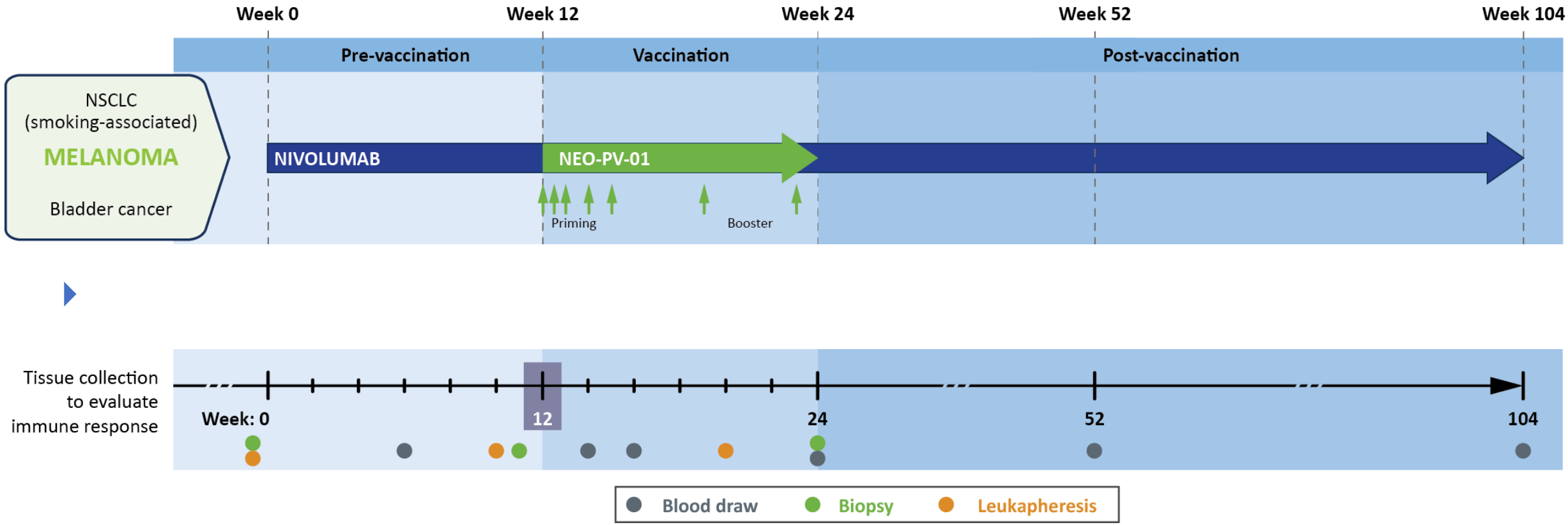


Hu Z & Leet DE *Nat. Med.*, 2021

Summary 1

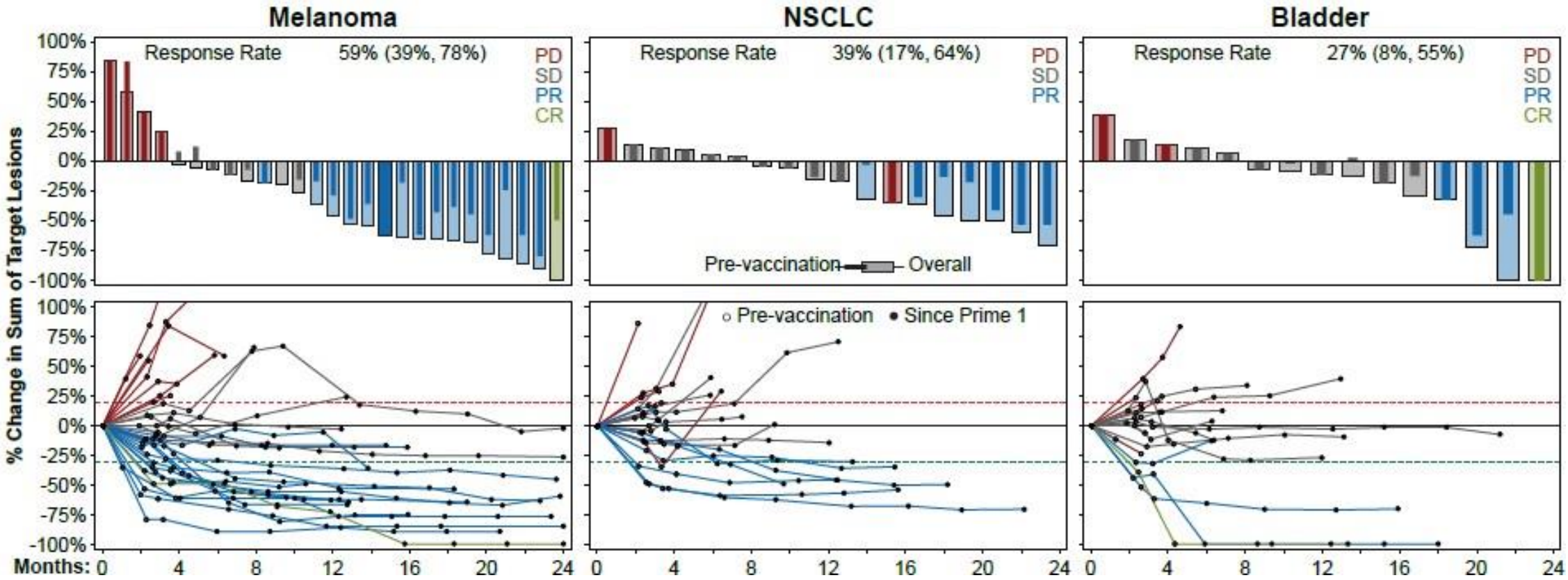
- Vaccine-induced neoantigen-specific $CD4^+$ T cells exhibit memory and cytotoxic signatures
- Neoantigen-specific T cell clones diversify over time
- Neoantigen-specific T cell responses persist long-term following vaccination
- Vaccine induced T cells can traffic to tumor sites

NT-001: Personalized peptide vaccine (PV-01) + Nivolumab in metastatic patients (melanoma, NSCLC, and urothelial cancer)



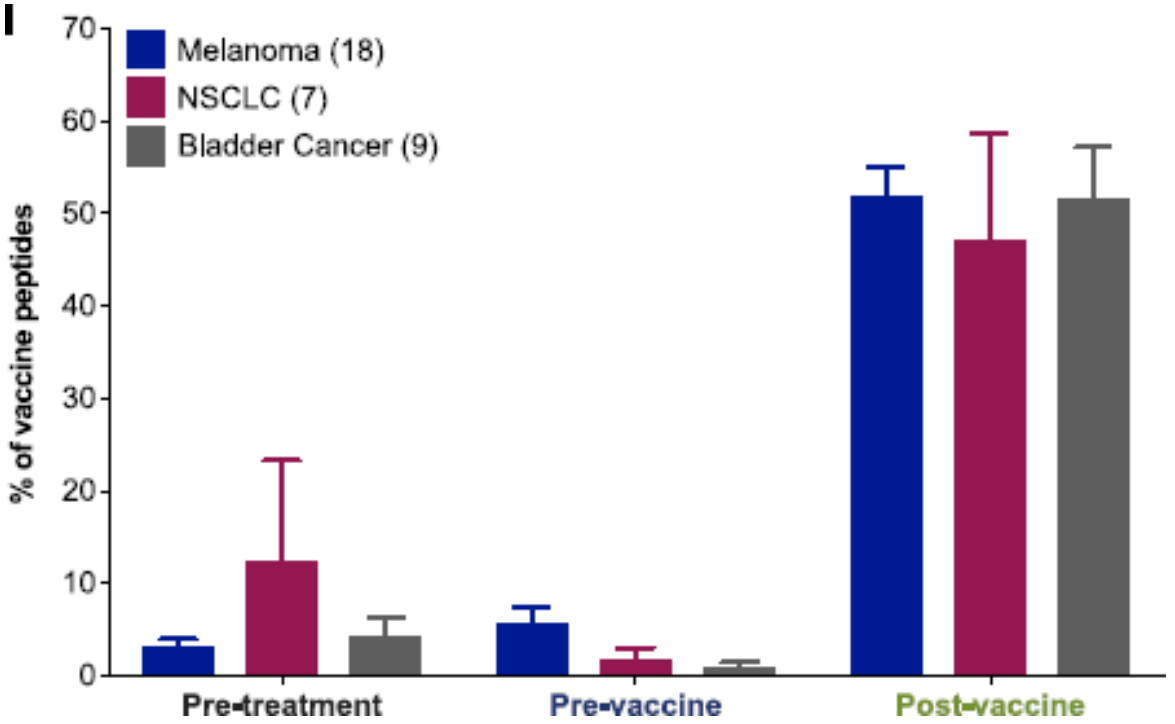
Ott et al. *Cell* 2020

NT-001: Clinical Responses



Ott et al. *Cell* 2020

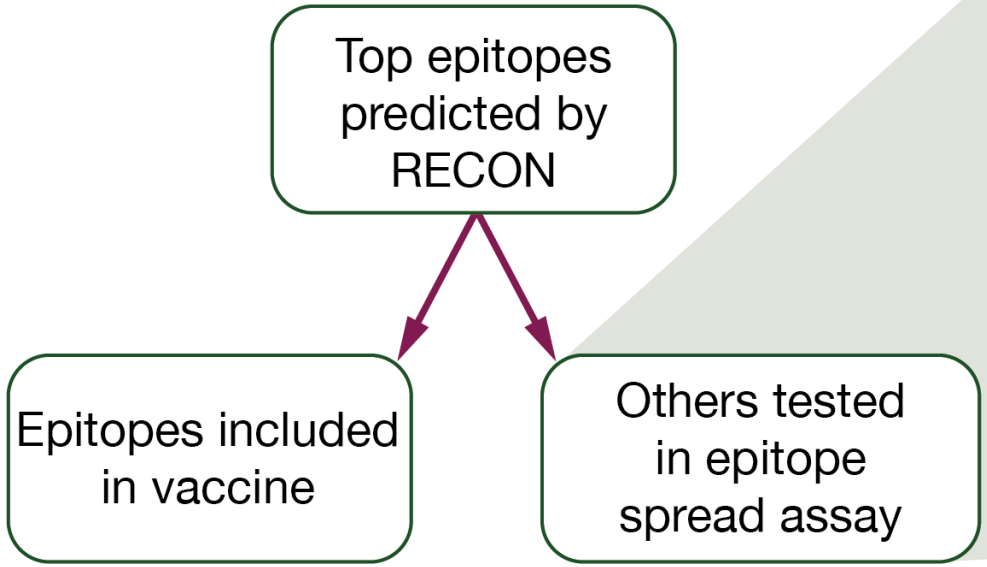
NEO-PV-01 + nivolumab induces neoantigen-specific immune responses



Ott et al. *Cell* 2020

NEO-PV-01 + NIVOLUMAB RESULT IN EPITOPE SPREAD TO MULTIPLE NEOANTIGENS

Generation of Patient-Specific Non-Vaccinated Neoantigens

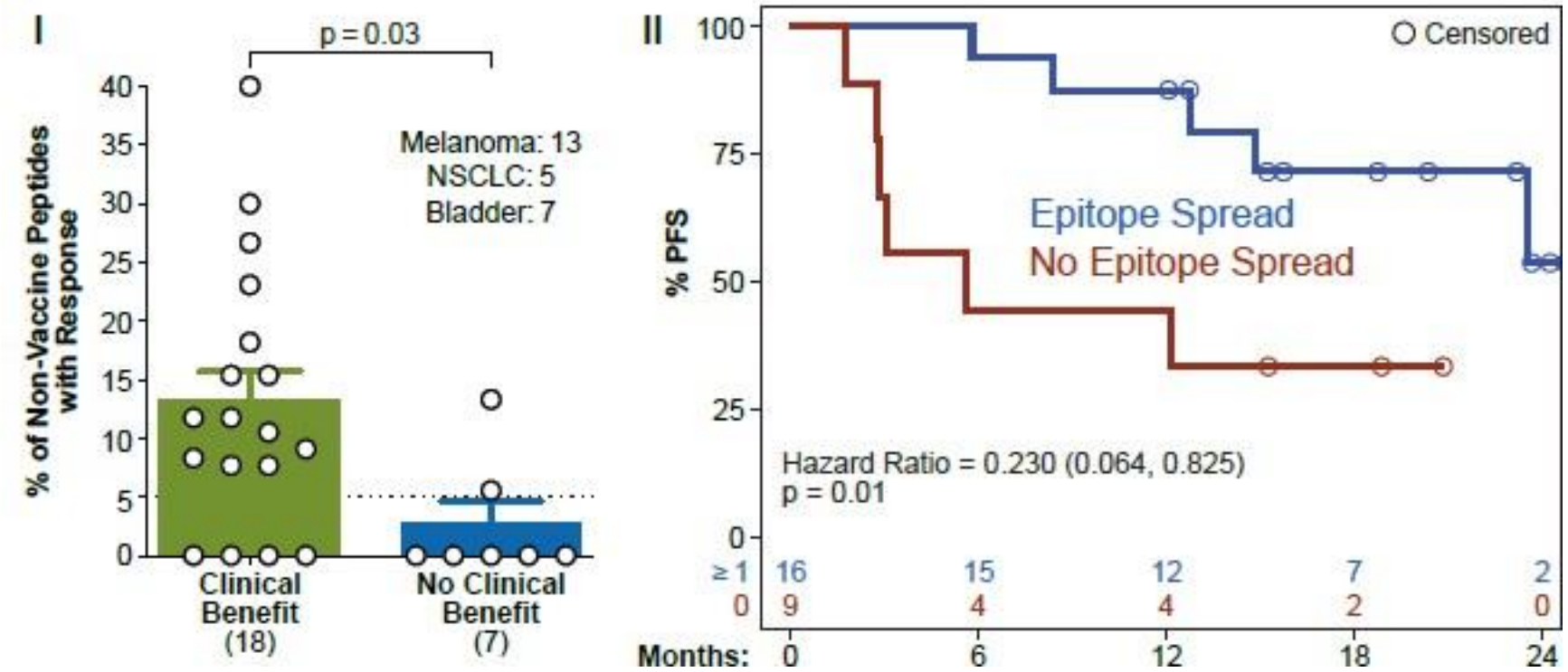


Observed in 7 out of 9 patients tested

Epitope Spread Peptide Analysis			
Subject	**# Epitopes Tested**	**# Positive Responses**	**36-Week DCB**
M1	15	5	Yes
M2	12	1	Yes
M5	13	1	Yes
M6	13	5	Yes
M10	19	2	Yes
M12	12	1	Yes
M13	13	2	Yes
M14	11	3	Yes
M3	18	0	No
M4	15	2	No

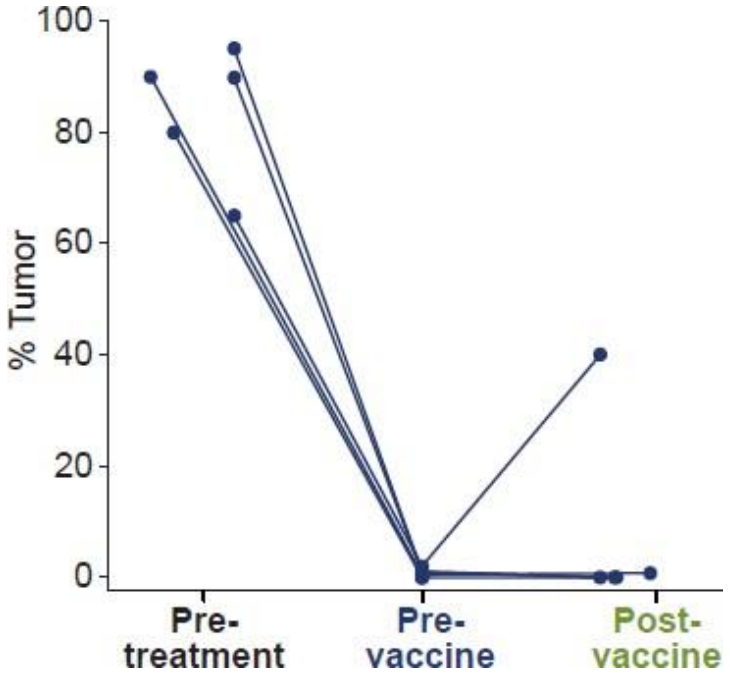
Hu-Lieskovan, Ott, ….Srinivasan, *AACR* 2019

Epitope spreading correlates with durable clinical benefit



Ott et al. *Cell* 2020

Pathologic response post vaccine is associated with clinical benefit



%PFS

Ott et al. *Cell* 2020

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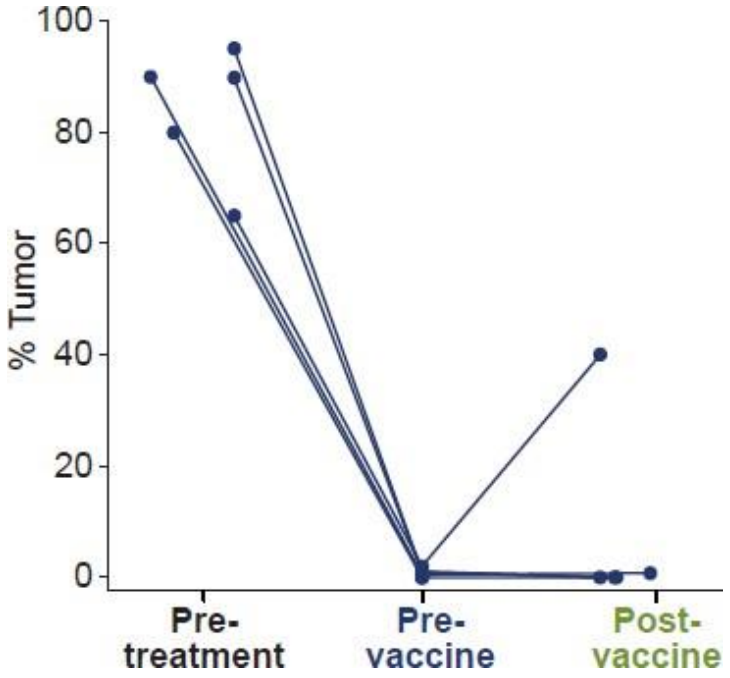

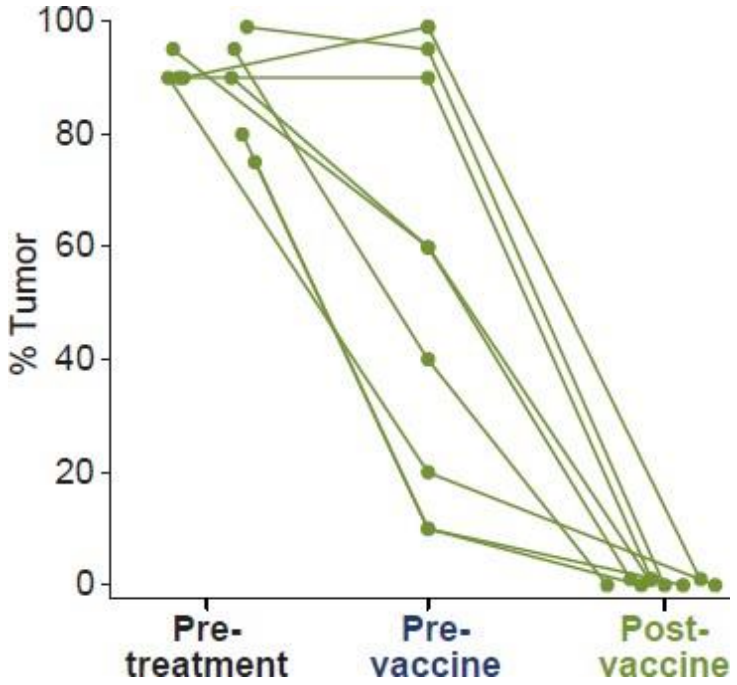

Ott et al. *Cell* 2020

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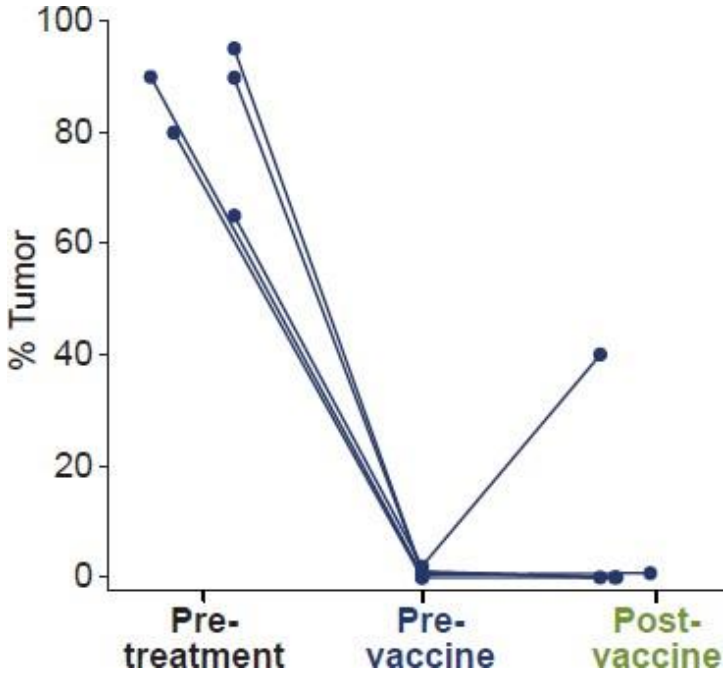
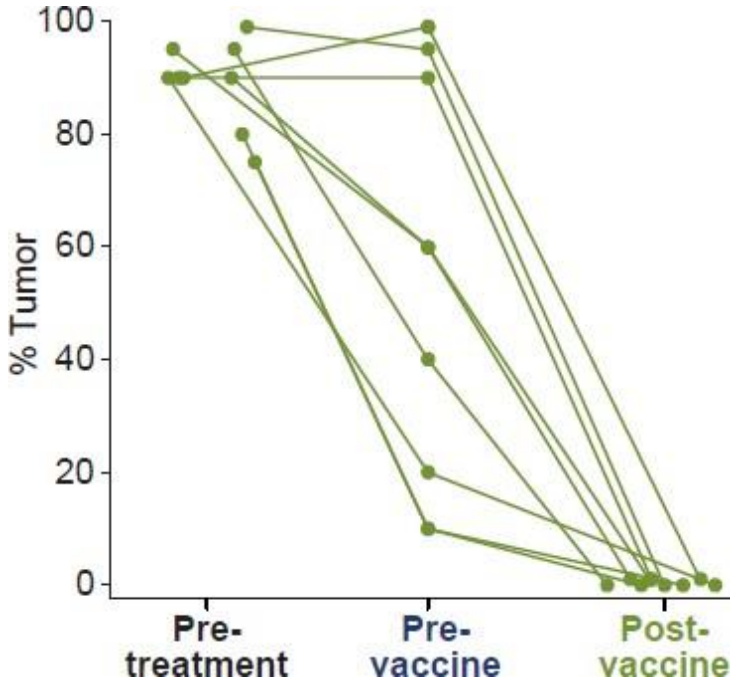
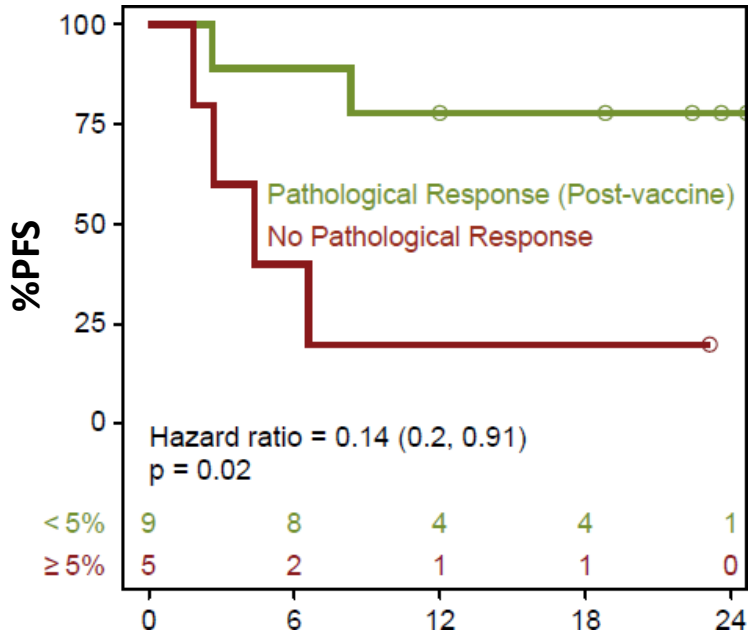






Ott et al. *Cell* 2020

Ongoing Clinical Trials Testing Neoantigen Targeted Vaccines

Vaccine (format)	Number of neoantigens included	Neoantigen discovery platform	Adjuvant and/or delivery system	Study phase	Tumour types	Treatment approach	ClinicalTrials.gov identifier (Ref.)[a]
NeoVax (SLP)	7–20	Broad Institute/DFCI pipeline[65,69,142]	Poly-ICLC	Pilot	Completely resected advanced-stage RCC	NeoVax plus locally administered ipilimumab (anti-CTLA4 antibody)	NCT02950766
				Phase Ib	Advanced-stage melanoma	NeoVax plus nivolumab (anti-PD-1 antibody) and locally administered ipilimumab	NCT03929029
GEN-009 (SLP)	4–20	ATLAS[133]	Poly-ICLC	Phase I/IIa	Melanoma, NSCLC, HNSCC, RCC or urothelial carcinoma	GEN-009 alone for patients who have no evidence of disease after completion of curative-intent treatments and with nivolumab or pembrolizumab (anti-PD-1 antibody) for those with unresectable advanced-stage tumours	NCT03633110 (REF.[116])
PGV001 (SLP)	Up to 10	Personalized genomic vaccine pipeline (Openvax)[144]	Poly-ICLC	Phase I	Advanced-stage solid tumours	PGV001 alone	NCT02721043 (REF.[145])
AutoSynVax (ASV), also known as AGEN2003 (SLP with recombinant HSP70)	Up to 24	AIM	QS-21 Stimulon	Phase Ia	Advanced-stage solid tumours	AutoSynVax alone	NCT02992977 (REF.[146])
RO7198457, also known as iNeST (RNA–lipoplex)	Up to 20	Not disclosed	NA	Phase Ib	Advanced-stage solid tumours, most commonly NSCLC, TNBC, melanoma and CRC	RO7198457 alone or with atezolizumab (anti-PD-L1 antibody)	NCT03289962 (REF.[117])
				Randomized phase II	ctDNA-positive resected stage III NSCLC	RO7198457 plus atezolizumab vs atezolizumab alone, after adjuvant chemoradiotherapy	NCT04267237
				Randomized phase II	Advanced-stage melanoma (treatment-naive)	RO7198457 plus pembrolizumab vs pembrolizumab alone	NCT03815058

Vaccine (format)	Number of neoantigens included	Neoantigen discovery platform	Adjuvant and/or delivery system	Study phase	Tumour types	Treatment approach	ClinicalTrials.gov identifier (Ref.)[a]
VB10.NEO (plasmid DNA)	Up to 20	NeoSELECT	PharmaJet Stratis injection system	Phase I/IIa	Advanced-stage RCC, HNSCC, melanoma or NSCLC without a complete response to SoC immune-checkpoint inhibitor therapy	VB10.NEO plus bempegaldesleukin (pegylated IL-2, a CD122-preferential IL-2 pathway agonist)	NCT03548467 (REF.[146])
GNOS-PV02 (plasmid DNA)	>50	Not disclosed	INO-9012 (plasmid encoding IL-12); CELLECTRA delivery device (in vivo electroporation)	Phase I	Newly diagnosed *MGMT* promoter-unmethylated glioblastoma	GNOS-PV02 alone following SoC surgery and/or radiotherapy	NCT04015700
				Phase I/II	Advanced-stage hepatocellular carcinoma	GNOS-PV02 plus pembrolizumab, folllowing disease progression or intolerance of SoC TKI therapy	NCT04251117
Granite (GRT-C901 adenovirus-based prime plus GRT-R902 RNA-based booster)	Up to 20	Edge	NA	Phase I/II	NSCLC, CRC (MSS), gastroesophageal adenocarcinoma, urothelial carcinoma or PDAC	Granite alone	NCT03794128
				Phase I/II	NSCLC, CRC (MSS), gastroesophageal adenocarcinoma or urothelial carcinoma	Granite plus nivolumab and ipilimumab	NCT03639714
mRNA-4157 (lipid encapsulated RNA)	Up to 20	Proprietary algorithm	NA	Phase I	Advanced-stage solid tumours	mRNA-4157 alone for patients with resected tumours or with pembrolizumab for those with unresectable tumours	NCT03313778 (REF.[118])
				Phase I	Resected high-risk melanoma (stage III)	mRNA-4157 plus pembrolizumab	NCT03897881
Not specified (DNA)	Not specified	Not disclosed	Intramuscular TriGrid Delivery System (TDS-IM)	Randomized phase I	Stage II or III TNBC	Vaccine vs vaccine plus durvalumab (anti-PD-L1 antibody), following SoC therapy	NCT03199040
			TDS-IM	Phase I	Resectable PDAC	Vaccine alone, following surgery and adjuvant chemotherapy	NCT03122106

Peptide

RNA

DNA

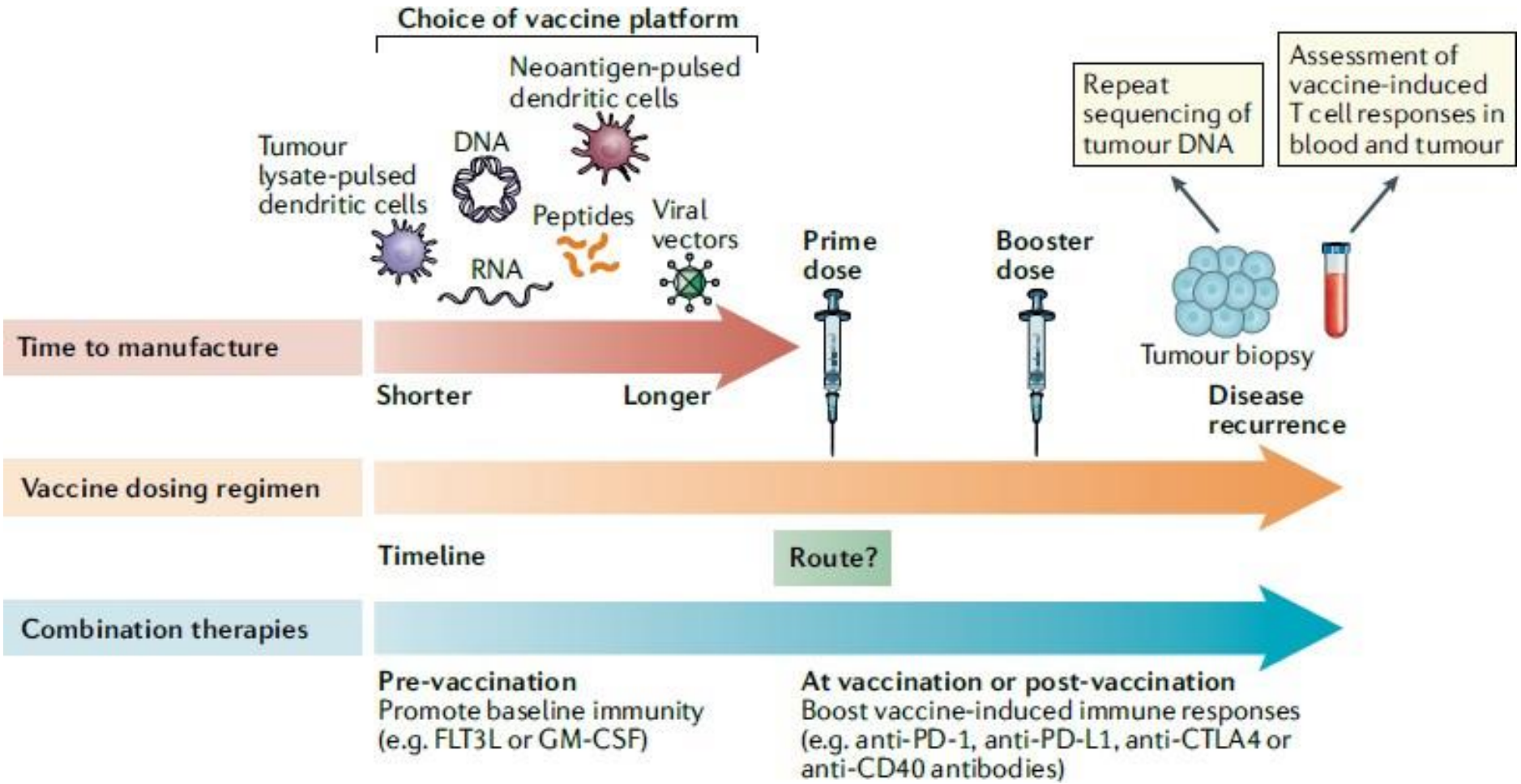
Viral

Blass, Ott *Nature Rev Clin Oncol*, 2021

Summary 2

- Vaccines can drive T cells to metastatic tumors
- Neoantigen peptide vaccines are feasible, safe, and immunogenic in patients with advanced melanoma and other solid tumors
- Clinical Response Data are encouraging, but not definitive
- Epitope spreading suggests on-target vaccine-induced tumor cell killing and is associated with progression-free survival
- Major Pathologic responses occur after vaccination and are also associated with progression-free survival
- Various Vaccine Platforms are in Development

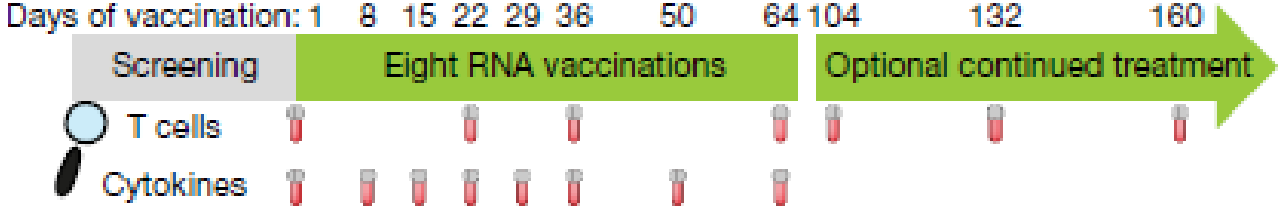
Considerations relating to therapeutic neoantigen vaccine regimens

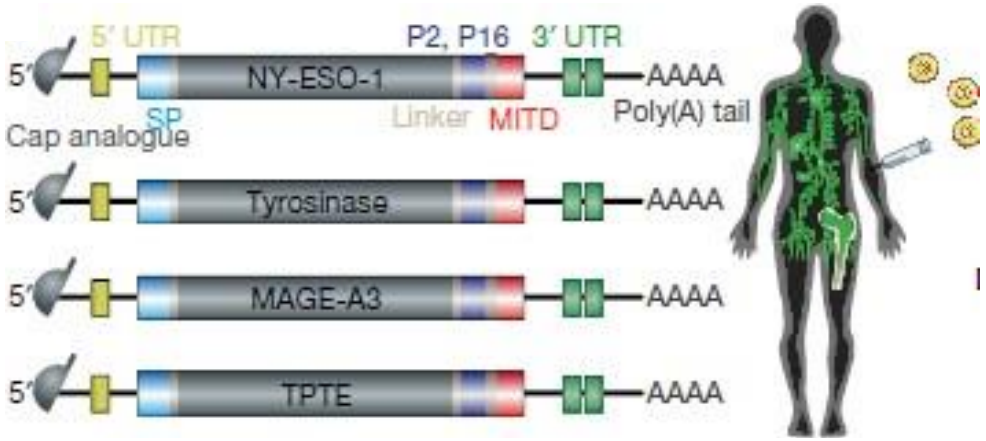


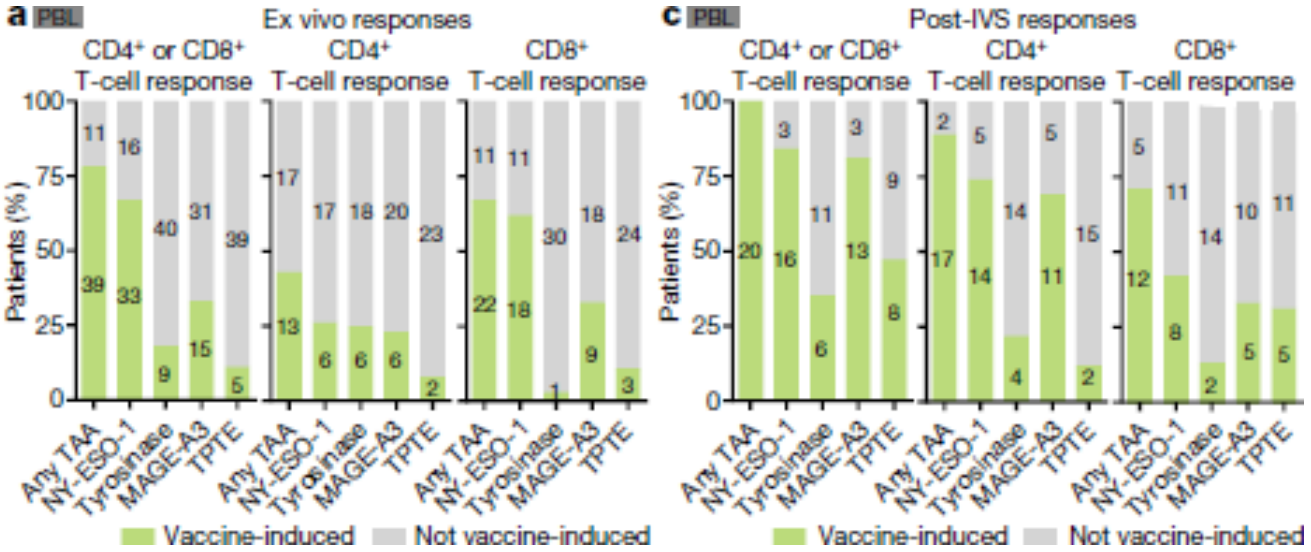
Blass, Ott *Nature Rev Clin Oncol*, 2021

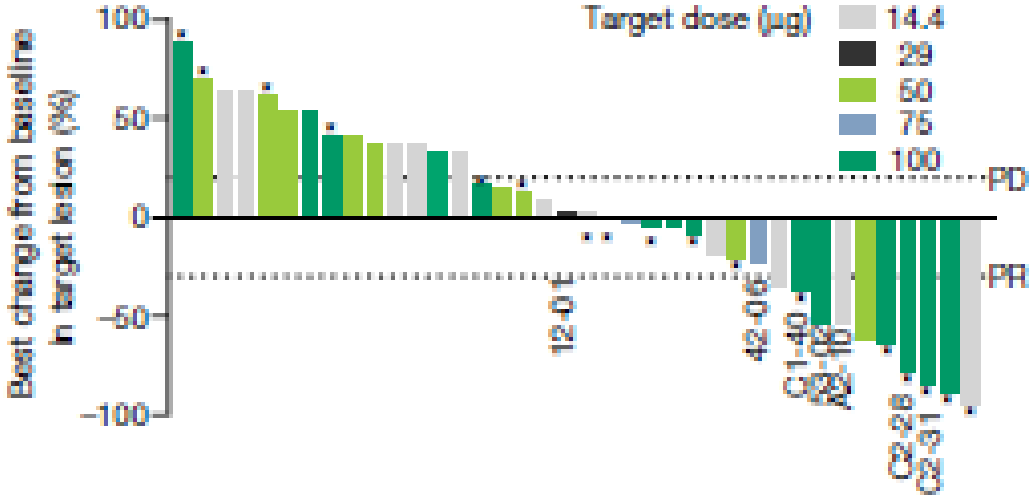
The “Lipo-MERIT” trial

Patient population	Trial design
- Advanced melanoma	- RNA-LPX vaccine, four non-mutant TAAs
- Resected and unresected III B/C, IV	- 3+3 intra-patient dose escalation
- Expression of at least one vaccine TAA	- Dose range (7.2–400 µg total RNA)
- Radiologically measurable and non-measurable disease	- Seven dose cohorts, three expanded cohorts
	- Prime/repeat boosts, with or without anti-PD1









Sahin, *Nature*, 2020

BLAVATNIK FAMILY FOUNDATION

Melanoma Research Alliance

National Heart Lung and Blood Institute
People Science Health

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

THE BRIDGE PROJECT

THE G. HAROLD AND LEILA Y. MATHERS FOUNDATION

NATIONAL CANCER INSTITUTE

Ben and Catherine Ivy Foundation

Emerson Collective

Catherine Wu lab

Zhuting Hu
Donna Leet
Ed Fritsch
Giacomo Olivera
Sachet Shukla
Jing Sun
Wandi Zhang
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Satyen Gohil
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